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The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, *etc*. The *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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SYSTEMATIC REVIEWS

Frequency, localization, and types of gastrointestinal stromal tumor-associated neoplasia

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Abstract

BACKGROUND

In recent years, increasing evidence of second neoplasms associated with gastrointestinal stromal tumors (GIST) has been found. Numerous case reports, mostly retrospective studies and a few reviews, have been published. To our knowledge, however, no systematic review or meta-analysis of the existing data has been performed so far.

AIM

To prepare a compilation, as complete as possible, of all reported second tumor entities that have been described in association with GIST and to systematically analyze the published studies with regard to frequency, localization, and types of GIST-associated neoplasms.

METHODS

The MEDLINE and EBSCO databases were searched for a combination of the keywords GIST/secondary, synchronous, coincident/tumor, neoplasm, and relevant publications were selected by two independent authors.

RESULTS

Initially, 3042 publications were found. After deletion of duplicates, 1631 remained, and 130 papers were selected; 22 of these were original studies with a minimum of 20 patients, and 108 were case reports. In the 22 selected studies, comprising a total number of 12050 patients, an overall rate of GIST-associated neoplasias of 20% could be calculated. Most second neoplasias were found in the gastrointestinal tract (32%) and in the male and female urogenital tract (30%). The specific risk scores of GISTs associated with other tumors were significantly lower than those without associated neoplasias.

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CONCLUSION
In this first systematic review, we could confirm previously reported findings of a more than coincidental association between GIST and other neoplasias. The question whether there is an underlying causal association will need further investigation. Our data suggest that even GIST with a very low risk of disease progression should prompt screening for second neoplasia and subsequent frequent controls or extended staging.

Key words: Gastrointestinal stromal tumor; Associated; Secondary; Neoplasia; Tumor

Core tip: Gastrointestinal stromal tumors (GIST) associated neoplasms have been previously reported to occur with a more than coincidental frequency. Numerous case reports, mostly retrospective studies and a few reviews have been published on this topic. In this, to our knowledge, first systematic review we analyzed 108 case reports and 22 retrospective and prospective studies with a total of 12050 patients. An overall rate of GIST-associated neoplasias of 20% could be calculated. Most second neoplasias were found in the gastrointestinal tract (32%) and in the male and female urogenital tract (30%).

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the digestive tract. Yearly incidence rates vary from 4.3 to 22 per million in different geographic regions, which may at least in part be caused by changing and improving diagnostic criteria and a lack of established GIST registries. In most studies, however, the yearly incidence is indicated as 10 to 15 per million[1], fulfilling the criterion of a rare disease. Median age at diagnosis is reported to be between 60 and 69 years in most studies[1,2]. GIST are considered to develop from interstitial cells of Cajal (ICC), which play an important role in autonomous gastrointestinal movement[3]. The most common localization of GIST is the stomach, followed by other gastrointestinal tract localizations[2,4].

Several driver mutations have been identified as playing an essential role in the development of GIST. The most frequent mutation can be found in the tyrosine kinase receptor c-kit (c-KIT), which accounts for 70%-80% of GIST[5-7] and is nowadays the most important target of medical tumor therapy in GIST patients. Other relevant mutations can be observed in the platelet-derived growth factor receptor alpha (PDGFR-α) in 5%-10%[5-7] and, in rare cases, in other genes such as neurofibromin 1 (NF1), succinate dehydrogenase (SDH), or BRAF[6,8].

GIST can occur in the setting of genetic syndromes such as neurofibromatosis 1[9], Carney triad[10], or familial GIST[11] and, in these cases, frequently come along with other benign or malignant neoplasias. In recent years, though, there has been increasing evidence of second neoplasia in patients with sporadic GIST[12-15]. Several retrospective studies and case series have been published on this topic, complemented by many case reports and a few reviews, but so far to our knowledge, no meta-analysis or systematic reviews have been conducted. The aim of this first systematic review is to prepare a compilation, as complete as possible, of all reported second tumor entities that have been described in association with GIST and to systematically analyze the published studies with regard to frequency, localization, and types of GIST-associated neoplasms.

MATERIALS AND METHODS

Literature research

We performed a literature search in the MEDLINE and EBSCO databases, using the keywords GIST/secondary, synchronous, coincident/tumor, neoplasm. All results were transferred to the citation manager Endnote® and duplicates were deleted. The remaining results were screened by two authors with regard to suitable topic, language, and publication standard. Discrepancies were resolved after discussion with a senior third author. Case reports and case series/studies in English or German were included. Only data that was fully published was eligible. Syndromic settings as familial GIST or neurofibromatosis were excluded as well as cases involving children. Studies had to include at least 20 patients, and studies that investigated only one specific kind of second neoplasm were excluded. Second neoplasms were considered regardless of the time frame between their occurrence and the occurrence of GIST. Malignant as well as benign second neoplasms were selected. In addition, the bibliographies of all selected papers that were published between 2016 and 2019 were screened for suitable references, as were the six published reviews on this topic.

Statistical analysis

For statistical calculations, we used SigmaPlot 13.0 (Systat, Erkrath, Germany) and Microsoft Excel (Microsoft Office 16). The chi-squared test was performed for testing the relationship between two categorical variables. A ^{a}P-value of < 0.05 was considered significant.

PROSPERO registration

Before starting the literature research, a registration of this systematic review in the international Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42019122784) was performed.

RESULTS

The literature search revealed a total of 3042 publications before February 2019. After deletion of duplicates, 1631 papers remained. Screening by the two authors (Waidhauser J and Bornemann A) resulted in 126 eligible papers. In addition, one study on 188 GIST patients that was performed at our institute by Mayr *et al*[15] and had not been published by the time of the literature search was included. Of the 130 selected publications, 108 were case reports and 22 were case series or retrospective and prospective studies (Figure 1).

All additional neoplasms that were reported in the case reports are listed in Table 1. The most frequent types were gastric and colorectal adenocarcinomas.

Among the 22 retrospective and prospective studies, a total of 12050 patients were included. Basic information on these studies is summarized in Table 2. The number of patients in which an additional tumor to the GIST diagnosis was found was 2426 (20.1%). The median age at the diagnosis of GIST was 63 years in the total study population and 68 years in those patients with an additional tumor. The male-to-female ratio was 1.1:1 in the total population and 1.4:1 in the GIST with secondary neoplasia group. The chi-squared test revealed a significant difference for the sex distribution of $P < 0.001$ with a predominance of male gender in cases with associated neoplasia (Table 3).

Of 2248 patients, for whom the respective data were available, 253 benign (11%) and 1995 (89%) malignant neoplasias were reported, with the restriction that in some studies, only patients with malignant second neoplasias were included. Chronological considerations revealed that 50% (366 of 732) of second neoplasias occurred synchronously to GIST, 26% (187 of 732) occurred before GIST, and 24% (179 of 732) were diagnosed after GIST. Focusing on synchronous second neoplasias, a rate of 6% (366 of 5131) was detected among all GIST patients. Of these synchronous second neoplasias 77% (177 of 230) occurred in the GI-Tract and 7% (16 of 230) in the male and female urogenital tract. The distribution of different histological subtypes (spindle *vs* epithelioid *vs* mixed) revealed no differences between the GIST-only patients and the patients with another neoplasm (spindle: 78% *vs* 80%; epithelioid: 8% *vs* 6%; mixed: 14% *vs* 14%) (Table 4).

Figure 2 gives an overview of the different localizations of the GIST-associated neoplasias. The most common manifestation was seen in the gastrointestinal tract (32%), followed by urogenital and female genital tract (30%); 10% of additional tumors were found in the breast and 6% each in the lung and in the blood and lymphatic system.

Regarding the risk scores for disease progression or recurrence of GIST, there was a significantly ($P < 0.001$) higher proportion of very low- and low-risk GIST in patients

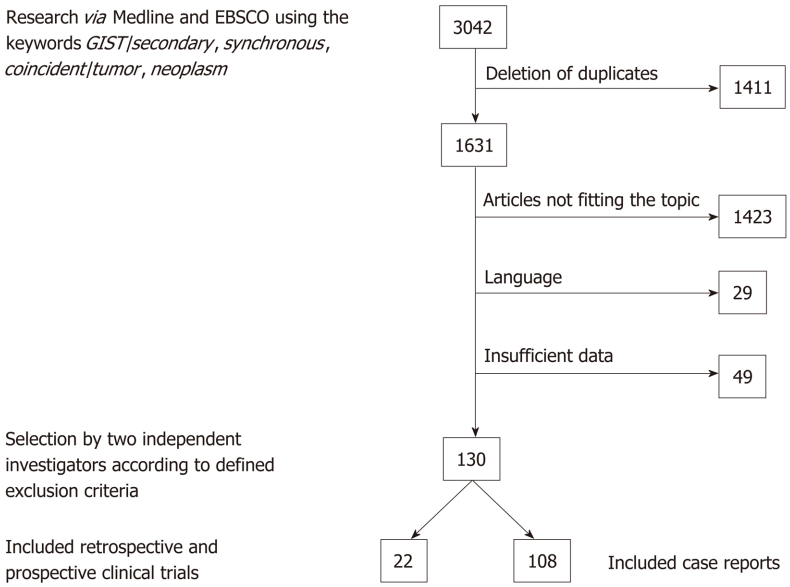

Figure 1 Flow of analysis based on the retrieved literature. GIST: Gastrointestinal stromal tumors.

with an additional tumor (65%) compared to the GIST-only group (35%), whereas in this latter group, the portion of intermediate and high-risk patients was higher (69% *vs* 31%). For calculation, we used the risk scores as they were applied in the different studies, which were most frequently those according to Fletcher *et al*[4] or Miettinen *et al*[16] (Table 5).

The mutational status of driver genes in patients with GIST and associated neoplasias was reported in only four of the 22 studies, with a total of 167 patients. These patients with GIST and second tumors showed mutations in exon 11 of the KIT gene in 69%, non-exon-11 mutations of the KIT gene in 6%, mutations in the PDGFR-α gene in 13%, and a "wildtype" status in 13%.

Data on follow-up was very heterogeneously reported or not available in most of the included studies, which is why even a descriptive analysis was not feasible.

DISCUSSION

In our systematic review, we detected a rate of 20.1% of second neoplasias in GIST patients, with the most frequent localization of associated tumors in the gastrointestinal tract and in the urogenital and female genital tract. Previously described rates of GIST-associated neoplasias varied between 11% and 50%[13,17]. The general probability of being diagnosed with cancer twice in a lifetime is estimated between 2% and 17% (syndromic settings or familial predisposition included)[18] or in other words with a chance of 1:9[12,19]. Compared to this number the rate of second neoplasias we found in GIST patients is obviously higher than expected. Several reasons can be considered accountable for the development of multiple tumors in one patient, for example, similar risk factors, environmental factors, or genetic predisposition, but also the higher likelihood of detection of another tumor within the examinations for staging or follow-up. In cases of sporadic GIST there are no definitely confirmed intrinsic risk factors or environmental factors. Genetic factors play a role in syndromes such as neurofibromatosis type I or Carney triad, but these patients were excluded in our study, and only patients with sporadic GIST were included. The occurrence of GIST-specific mutations such as in the c-KIT or PDGFRα gene that we found in the group of patients with GIST and second neoplasms were similar to those reported for GIST in general before[5-7].

The localization of GIST-associated neoplasias with the highest frequency in the gastrointestinal tract, the urogenital, and female genital tract is consistent with previously reported findings[20,21]. In addition to a possible common underlying predisposition, the probability of detecting even small GIST during staging examinations for gastrointestinal tract tumors might be higher than in cases of, for example, lung or head and neck tumors. This is might also be the explanation for the high rate of 77% of GI-tract localization in synchronous second neoplasias.

The median age of the total study population compared to the group of patients

Table 1 Case reports: Overview of tumor entities

Tumor entity	Ref.
Gastrointestinal Tract	
Gastric adenocarcinoma	[29-55]
Colorectal adenocarcinoma	[56-71]
Gastric high grade IEN	[72]
Esophagus SCC	[48,59,73]
Esophagus Small Cell Carcinoma	[39]
Gastro-esophageal junction adenocarcinoma	[74,75]
Duodenum adenocarcinoma	[76]
Papilla Vateri NET	[77]
Gastric Lipoma	[78]
Gastric NET	[79-82]
Doudenum NET	[67]
Ileum NET	[83]
Gastric Schwannoma	[84]
Colon NET	[85]
Jejunal Sarcomatoid Carcinoma	[86]
Pancreas adenosquamous carcinoma	[87,88]
Pancreas adenocarcinoma	[89,90]
Pancreas NET	[91-95]
Hepatocellular carcinoma	[96-99]
Cholangiocellular Carcinoma	[100,101]
Perivascular Epitheloid Cell Tumor Liver	[102]
Urogenital Tract	
Renal Cell Carcinoma	[103,104]
Renal Chromophobe Cell Carcinoma	[105]
Prostate Adenocarcinoma	[40,69,82,106,107]
Transitional Cell Carcnimona Bladder	[86]
Female Genitale Tract	
Ovarian Carcinoma	[108]
Ovarian Serous Adenocarcinoma	[109,110]
Uterus Leiomyoma	[91]
Breast	
Sarcoma	[111]
Invasive Ductal Carcinoma	[55,61,63,92]
Blood/ Lymphatic	
Acute Myeloid Leukemia	[112-114]
Acute Biphenotypic Leukemia	[100]
Chronic Lymphoid Leukemia	[115]
Low Grade B Cell Lymphoma Stomach	[116]
Extranodal DLBCL	[117,118]
Burkitt Lymphoma	[119]
Mantle Cell Lymphoma Appendix	[120]
MALT Lymphoma	[50,121]
Multiple Myeloma	[122]
Head and Neck	
Oral Melanoma	[123]
Papillary Thyroid Carcinoma	[124]
Lung	
Adenocarcinoma	[125-127]
SCC	[107]
NSCLC	[106]
Skin	

Melanoma	[128,129]
Squamous Cell Carcinoma	[130]
Merkel Cell Carcinoma	[131]
Soft Tissue	
Myxofibrosarcoma	[82]
Dermatofibrosarcoma	[132]
Ewing Sarkoma	[133]
Others	
Adrenocortical Carcinoma	[134]
Peritoneal Mesothelioma	[135]
Mesenterial Fibromatosis	[136]
Granular cell tumor	[55]

IEN: Intraepithelial neoplasia; SCC: Squamous-cell carcinoma; NET: Neuroendocrine tumor; DLBCL: Diffuse large B cell lymphoma; MALT: Mucosa associated lymphatic tissue; NSCLC: Non-small cell lung cancer.

who developed a second tumor showed a difference of five years at the time-point of GIST diagnosis, with the higher median age in the GIST with associated neoplasm group. A possible explanation for this finding could be the age-dependent risk increase for cancer in general[14]. Previously performed reviews on the topic of GIST and associated neoplasms mostly concentrated on the occurrence rate and localization of the associated tumors and, in some cases, on the outcome and follow-up[20-24]. Analysis of age or sex distribution have not been performed on larger numbers of patients. We found a significantly higher number of male patients who were diagnosed with GIST and a second neoplasia than in the total population of GIST patients. An equal sex distribution for GIST patients in general has been reported in the literature before[1]. Regarding the overall incidence of cancer worldwide, the sex distribution of patients diagnosed with cancer in 2018 is estimated at a male-to-female ratio of 1.1:1 (9.5 million new cases in men and 8.6 million new cases in women). Among gastrointestinal neoplasias, which were the most frequent GIST-associated neoplasias in our review, there is a difference in the worldwide incidence between men and women with a higher rate of gastrointestinal (GI) tumors diagnosed in men in 2018 (2.7 million cases in men *vs* 1.4 million cases in women)[25]. Whether there is a difference of distribution of the second neoplasias between sexes in our review population remains unclear. In most analyzed studies, the reported data was not sufficient to answer this question.

Several risk classification systems are used to assess the risk of disease progression or recurrence of GIST[4,16]. Most of them use the size, localization, and mitotic rate of GIST and are therefore, at least in part, comparable. By summarizing the risk categories in two groups (very low and low *vs* intermediate and high), we could find a significant difference between the GIST-only patients and those having GIST and another neoplasia by using the chi-squared test. The patients with GIST-associated neoplasias had lower risk scores, which might be due to a higher detection rate of even small GISTs with low risk scores in the setting of another neoplastic disease.

Since the establishment of targeted therapies for GIST with imatinib or second-line tyrosine kinase inhibitors, the prognosis even of advanced GIST has significantly improved[26]. On the other side, there is growing interest in the question of elevated risk of developing secondary neoplasia under the treatment with imatinib. Phan *et al*. found a higher rate of secondary tumors among GIST patients in the imatinib era than in the pre-imatinib era[27], although the most likely reason for this is the prolonged survival even of patients with advanced GIST, as it has been described by different authors[28]. Another point that relativizes the impact of imatinib on the development of secondary tumors can be seen in our review: About 75% of associated neoplasias were diagnosed either before GIST or synchronously with GIST; furthermore, not all patients with a GIST diagnosis in advance were treated with imatinib.

In summary, in this, to our knowledge first, systematic review on the topic of secondary neoplasia in patients with GIST, we confirm the previously described elevated number of associated neoplasms and the most common localizations of this neoplasms. We found a higher median age in the GIST with second neoplasia group and significantly more male patients who developed associated tumors, whereas the risk scores of GIST in this group were significantly lower. We conclude that even very low- and low-grade GISTs should be a reason to consider frequent controls or extended staging for early detection of second neoplasias, especially in the gastrointestinal and urogenital tract. To understand whether there is an underlying

Table 2 Retrospective and prospective studies used for this investigation

Author	Year	Date of diagnosis	N	Patient characteristics				Number (rate) of patients with ass. NPL	Organ systems affected by associated NPL										
				Age average (median)		Sex m/f			GI-tract	Liver/gall bladder/pancreas	Urogenital tract	Female genital tract	Breast	Blood/lymphatic system	Head and neck	Lung	Skin/melanoma	Soft	Other
				Total population	Pat. with ass. NPL	Total population	Pat. with ass. NPL												
Adim *et al*[137]	2011	1997-2009	78		62		9/4	13 (17%)	9	2	1		1						
Agaimy *et al*[14]	2005	1997-2004	97	65	72	42/55	6/12	18 (17%)	6	3	2	3	2	2		2			
Aghdassi *et al*[138]	2018	1993-2011	104	67		54/50		44 (42%)	16	4	8		7	2				1	
Amaadour *et al*[139]	2013	1998-2006	43	62	65	15/28	1/5	6 (14%)	5				1						
Fernandez *et al*[140]	2018	1999-2016	104		64	62/42	22/10	32 (31%)	9	4	7		3	3	2	2	1	1	
Ferreira *et al*[141]	2010	1998-2006	43	62	61	15/28	1/5	6 (14%)	5				1						
Giuliani *et al*[142]	2012	2002-2010	24	66	69	12/12	5/3	8 (33%)	6		1		1						
Gonalves *et al*[143]	2010	1998-2008	101		68		5/9	14 (14%)	8		2	2	1						1
Hechtmann *et al*[144]	2015	2009-2013	260		65	142/118	30/20	50 (19%)	2		21	1	8	8	7	1	3	3	6
Kramer *et al*[17]	2015	2006-2011	836	68	69	423/413	148/119	422 (51%)	118	20	60	22	26	23	6	8	23	2	9
Lai *et al*[145]	2016	1995-2015	749		68		77/59	136 (18%)	64	27	12	10	7	1	9	13	4	3	10
Liszka *et al*[146]	2007	1989-2006	82		64	38/44	12/10	22 (27%)	17	5				1					
Mayr *et al*[15]	2019	1998-2017	188		69			70 (37%)	23	1	17	9	5	5		2	5		3
Murphy *et al*[12]	2015	2001-2011	6112			3252/2860	727/481	1047 (17%)	208	34	432		144	80	54	99	52	48	72

Pandurengan *et al*[147]	2010	1995-2007	783	57		444/339	91/62	153 (20%)	40	8	48	14	15	12	1	10	9	9	20
Ponti *et al*[148]	2010	1988-2007	141	66	67	77/64	20/26	46 (33%)	18	1	7	2	6	1		2	1	2	3
Richter *et al*[149]	2008	1993-2005	54	65		28/26		13 (20%)	7		3		1	1					1
Rodriquenz *et al*[150]	2016	2002-2014	128	65	68	59/69	19/27	46 (34%)	24	5	3	4	2	1	1	3		3	1
Rubio-Casadevall *et al*[151]	2015	1996-2006	132	65		67/53		30 (23%)	8	2	3	1	3			3			
Sevinc *et al*[152]	2011	2002-2009	200		67		20/12	32 (16%)	16		5	1	2	1	2			1	4
Smith *et al*[13]	2016	2001-2009	1705	63	69	885/820	95/86	181 (11%)											
Vassos *et al*[153]	2014	2000-2009	86	66	70	50/36	27/10	37 (43%)	19	7	5			4	3		3	1	
			12050	63	68	1.1 : 1	1.4 : 1	2426 (20,1%)	751 (32%)		706 (30%)		236 (10%)	145 (6%)	85 (4%)	145 (6%)	101 (4%)	74 (3%)	130 (5%)

genetic cause for the elevated rates of GIST-associated neoplasias, further studies will be needed.

Table 3 Age and sex distribution

	Total study population	GIST with associated neoplasia	No. of patients available for calculation
Age (median)	63	68	4176/1139
Sex male: Female	1.1:1	1.4:1	10444/2080

GIST: Gastrointestinal stromal tumors.

Table 4 Characteristics of gastrointestinal stromal tumors and associated neoplasias

Parameter	Quantification		No. of patients available for calculation
Designtion of associated NPL, *n* (%)	Benigne 253 (11)		2248
	Malignant 1995 (89)		
Chronological presentation, *n* (%)	Synchoronous 366 (50)		732
	GIST first 179 (24)		
	Ass. NPL first 187 (26)		
Histological subtypes of GIST, *n* (%)	Spindle	Total population 409 (78)	525; 185
		GIST + ass. NPL 149 (80)	
	Epitheloid	Total population 43 (8)	
		GIST + ass. NPL 11 (6)	
	Mixed	Total population 73 (14)	
		GIST + ass. NPL 25 (14)	

GIST: Gastrointestinal stromal tumors.

Table 5 Distribution of risk scores, *n* (%)

Risk score	GIST without associated neoplasia	GIST with associated neoplasia	Total
Low and very low	123 (35)	230 (65)	353
Intermediate and high	373 (69)	165 (31)	538
Total	496	395	891

GIST: Gastrointestinal stromal tumors.

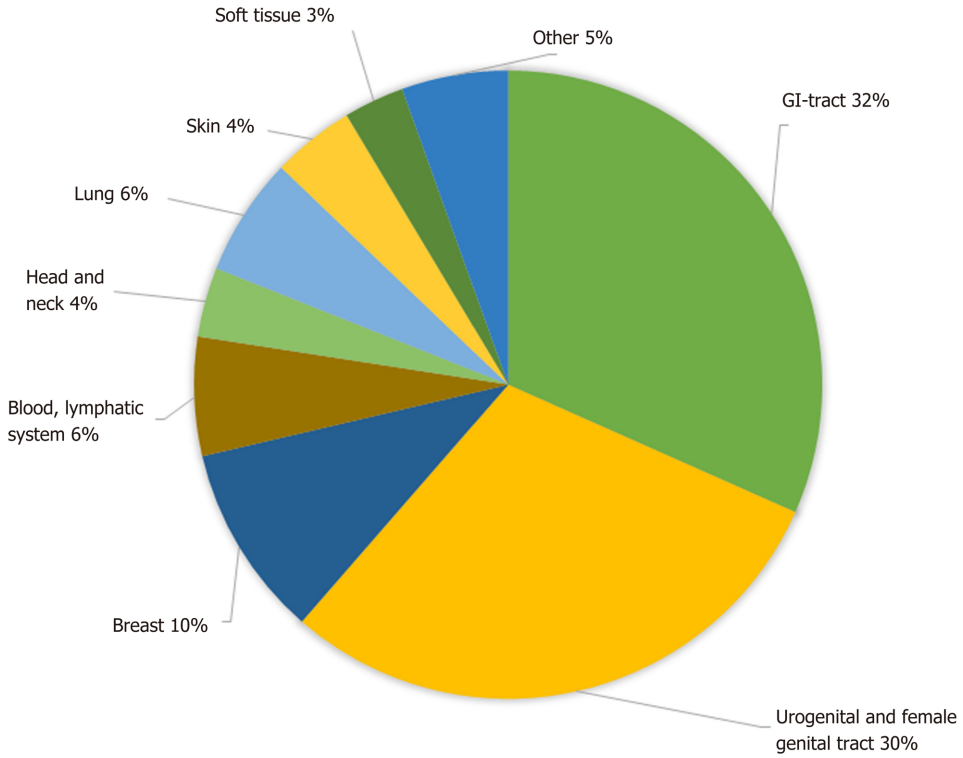

Figure 2 Localization of gastrointestinal stromal tumor-associated neoplasias. GI: Gastrointestinal.

ARTICLE HIGHLIGHTS

Research background

In recent years, numerous case reports, mostly retrospective studies and a few reviews on the topic of second neoplasias associated with gastrointestinal stromal tumors (GIST) have been published. To our knowledge, however, this is the first systematic review of the existing data.

Research motivation

The aim of this review was to prepare a compilation, as complete as possible, of all reported second tumor entities that have been described in association with GIST, and to systematically analyze the published studies with regard to frequency, localization, and types of GIST-associated neoplasms.

Research objectives

The main focus of this review was on frequency, localization, dependence of gender, age and risk classification of GIST associated neoplasias. Summarizing the data of a large number of patients could especially help in the daily clinical work with GIST patients.

Research methods

The MEDLINE and EBSCO databases were searched for a combination of the keywords GIST/secondary, synchronous, coincident/tumor, neoplasm, and relevant publications were selected by two independent authors. All case reports were summarized according to the reported tumor entity and included clinical studies were analyzed with regard to the previously mentioned topics.

Research results

Of the initially found 3042 publications, 130 papers were selected; 22 of these were original studies, and 108 were case reports. In the 22 selected studies, comprising a total number of 12050 patients, an overall rate of GIST-associated neoplasias of 20% could be calculated. Most second neoplasias were found in the gastrointestinal tract (32%) and in the male and female urogenital tract (30%). The male-to-female ratio revealed a predominance of male gender in cases with associated neoplasia. The specific risk scores of GISTs associated with other tumors were significantly lower than those of GIST without associated neoplasias. The question if there are specific genetic mutations that occur with a higher frequency in GIST patients with second tumors could not be answered and would be an interesting topic for future research.

Research conclusions

GISTs are associated with other neoplasias with a rate of 20% and occur most frequently in the gastrointestinal and urogenital tract. This confirms previous findings on a larger number of

patients. GIST associated neoplasias occur with a higher likelihood in older, male patients with low grade GIST. 50% of GIST associated neoplasias are detected synchronously. Our findings should be a reason to consider frequent controls or extended staging for early detection of second neoplasias, especially in the gastrointestinal and urogenital tract.

Research perspectives

If there is a causal relation between GIST and second tumors remains unclear. As data on genetic mutations of the GIST were reported very heterogeneously focusing on this topic could be an interesting point for future research.

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